Kopsine and Danuphylline Alkaloids from *Kopsia.* Biomimetic Partial Synthesis of Danuphylline B

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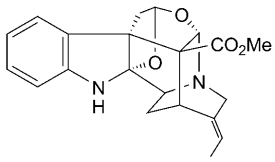
Two new indole alkaloids, 12-methoxykopsine (**6**) and danuphylline B (**7**), were obtained from the leaf extract of the Malayan *Kopsia* species, *K. arborea*, and their structures established by spectroscopic analysis. An electrochemically-mediated partial synthesis of the ring-opened alkaloid, danuphylline B from the hexacyclic alkaloid, methyl *N*(1)-de(methoxycarbonyl)chanofruticosinate was carried out.

Introduction. – The genus *Kopsia* (Apocynaceae) which is widely distributed in Southeast Asia [1] has proven to be a fertile source of novel alkaloids with intriguing carbon skeletons as well as interesting biological activities [2–27]. We previously reported several indoles characterized by unusual carbon skeletons from *K. arborea* BLUME, such as the cage indole arbophylline (**1**) [2], the three-nitrogen pentacyclic indole arboflorine (**2**) [3], the tetracyclic indole mersicarpine (**3**) [4], and the regioisomeric tetracyclic indoles, arboricine (**4**), and arboricinine (**5**) [5]. Except for arbophylline (**1**), the alkaloids were isolated from the stem-bark extract. The leaf extract is characterized by a predominance of the methyl chanofruticosinate alkaloids, including the new prunufolines A–F [28]. We now report the isolation of two additional new alkaloids from the leaf extract, a methoxykopsine (**6**) and danuphylline B (**7**), as well as a partial synthesis of danuphylline B.

Results and Discussion. – Compound **6** was obtained from the leaf extract of *K. arborea* as a colorless oil, with $[\alpha]_D = +16$ ($c = 0.05$, $CHCl_3$). The MS showed a molecular ion at *m*/*z* 410, in addition to significant fragment ions observed at *m*/*z* 382 and 312 (base peak), attributed to the loss of C_2H_4 and $C_5H_4O_2$, respectively, which are characteristic of kopsine alkaloids [29]. HR-EI-MS measurements (*m*/*z* 410.1842) gave the molecular formula $C_{23}H_{26}N_2O_5$, which is in agreement with the observation of 23 C-atom resonances in the ^{13}C-NMR spectrum. The UV spectrum is typical of a dihydroindole chromophore (215, 244, and 289 nm), while the IR spectrum showed bands at 3422, 1753, and 1678 cm^{-1} due to OH, ketone and carbamate functions, respectively. The ^{1}H-NMR spectrum of compound **6** (*Table*) was generally similar to



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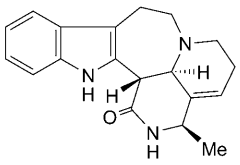

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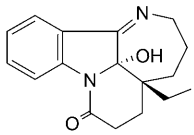

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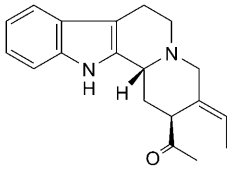

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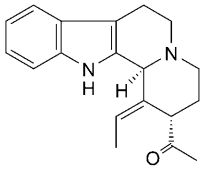

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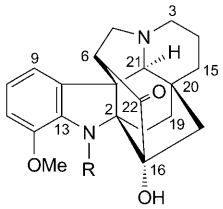
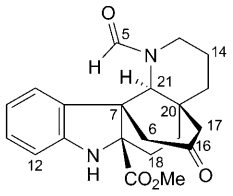


6 R = CO_2Me



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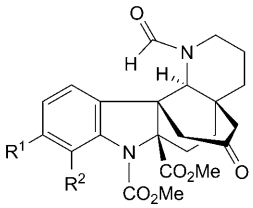
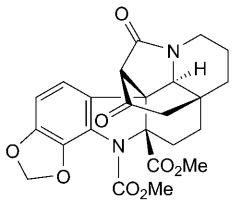


8 $R^1,R^2 = OCH_2O$
9 $R^1 = R^2 = H$



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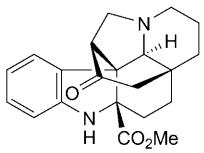

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that of kopsine, except for the aromatic region, which indicated substitution of C(9) or C(12) by a MeO group. This was apparent from the coupling pattern observed for the aromatic H-atoms as well as the presence of an additional MeO signal at δ(H) 3.83. However, the ^{1}H and ^{13}C chemical shifts of the aromatic moiety (*Table*) were consistent with 12-MeO substitution [30][31]. A further proof of 12-MeO substitution was the observation of reciprocal NOEs between H–C(9) and H–C(21). The structure of **6** was therefore determined as 12-methoxykopsine.

Danuphylline B (**7**) was also obtained from the leaf extract of *K. arborea* as a colorless oil, with $[\alpha]_D = +47$ ($c = 0.13$, $CHCl_3$). The UV spectrum showed absorption maxima at 212, 239, and 294 nm, suggesting the presence of a dihydroindole

Table. *[1]H- and [13]C-NMR Data for Compounds* **6** *and* **7** (400 MHz, $CDCl_3$)[a]). δ in ppm, J in Hz.

6			**7**		
	δ(H) (J in Hz)	δ(C)		δ(H) (J in Hz)	δ(C)
C(2)		76.6	C(2)		77.0
CH_2(3)	2.97–3.08 (*m*)	46.4	CH_2(3)	2.70–2.75 (*m*), 4.58 (*dd*, *J* = 12, 9)	34.7
CH_2(5)	3.16 (*dd*, *J* = 10, 5), 3.58 (*t*, *J* = 10)	53.8	H–C(5)	6.62 (*s*)	165.7
H–C(6)	2.70 (*dd*, *J* = 10, 5)	52.3	CH_2(6)	2.70 (*d*, *J* = 17), 2.85 (*d*, *J* = 17)	39.2
C(7)		61.0	C(7)		53.9
C(8)		138.0	C(8)		128.8
H–C(9)	7.08 (br. *s*)	115.0	H–C(9)	6.83–6.87 (*m*)	123.9
H–C(10)	7.14 (*t*, *J* = 8)	127.1	H–C(10)	6.83–6.87 (*m*)	119.9
H–C(11)	6.68 (*dd*, *J* = 8, 1)	112.2	H–C(11)	7.18 (*ddd*, *J* = 8, 7, 2)	129.3
C(12)		150.5	H–C(12)	6.83–6.87 (*m*)	
C(13)		130.7	C(12)		111.1
CH_2(14)	1.22–1.36 (*m*), 1.74–1.86 (*m*)	15.4	C(13)		148.9
CH_2(15)	1.22–1.36 (*m*), 1.47–1.56 (*m*)	34.9	CH_2(14)	1.70–1.79 (*m*), 1.90–2.00 (*m*)	19.2
C(16)		82.0	CH_2(15)	1.30 (*dt*, *J* = 14, 9), 1.61–1.67 (*m*)	29.8
CH_2(17)	1.59 (*d*, *J* = 15), 2.38 (*dd*, *J* = 15, 4)	43.4	C(16)		207.9
CH_2(18)	1.66 (*ddd*, *J* = 14, 12, 5), 2.46 (*ddd*, *J* = 14, 12, 5)	20.4	CH_2(17)	2.45 (*d*, *J* = 20), 2.72 (*d*, *J* = 20)	45.9
CH_2(19)	1.22–1.36 (*m*), 1.47–1.56 (*m*)	33.0	CH_2(18)	2.00 (*ddd*, *J* = 14, 5, 2), 2.18 (*ddd*, *J* = 15, 13, 6)	26.7
C(20)		31.9	CH_2(19)	1.61–1.67 (*m*), 1.90–2.00 (*m*)	39.0
H–C(21)	3.18 (br. *s*)	69.2	C(20)		34.0
C(22)		214.2	H–C(21)	3.68 (br. *s*)	59.7
12-MeO	3.83 (*s*)	53.6	CO_2Me	3.62 (*s*)	52.5
16-OH	7.00 (*s*)		CO_2Me		174.2
NCO_2Me	3.73 (*s*)	55.9			
NCO_2Me		156.4			

[a]) Assignments based on COSY and HMQC.

chromophore, while the IR spectrum showed bands due to NH (3347 cm^{-1}), ketone/ester (1731 cm^{-1}), and formamide (1661 cm^{-1}) functions. The EI-MS showed a molecular ion at *m/z* 368 with other significant fragment peaks at *m/z* 339 ($[M - CHO]^+$), 309 ($[M - CO_2Me]^+$), and 281 ($[M - CO_2Me - CH_2CH_2]^+$). The ^{13}C-NMR spectrum of **7** (*Table*) confirmed the presence of ketone (δ(C) 207.9), ester (δ(C) 174.2), and formamide (δ(C) 165.7) C=O groups. The ^{1}H-NMR spectrum of **7** showed the presence of an unsubstituted indole moiety from signals due to four contiguous aromatic H-atoms, a methyl ester function, two pairs of distinctive *AB doublet*s due to two isolated CH_2 groups, both in α-position to a ketone C=O group, in addition to a low field one-H *singlet* observed at δ(H) 6.62. The latter signal was associated with the formamide C=O resonance at δ(C) 165.7 from the HMQC spectrum, and this, coupled with the features mentioned earlier, and the notable absence of the C(5)–C(6) ethylene fragment suggested an alkaloid of the danuphylline group [21][22][32]. This was further supported by the observation of an unusually deshielded H–C(3) at δ(H) 4.58 due to anisotropy from the proximate formamide C=O group. Since the initial report of the prototype alkaloid of this group, danuphylline (**8**), a second congener, *i.e.*, the 11,12-de(methylenedioxy) derivative, danuphylline A (**9**), has been isolated from a Chinese *Kopsia* [32]. The NMR data of the non-indolic portion of **7** in fact showed a close correspondence to those of **8** [21][22] and **9** [32], suggesting departure from these two alkaloids in the indole moiety. HR-EI-MS measurements (*m/z* 368.1735) of **7**, which gave the molecular formula $C_{21}H_{24}N_2O_4$, suggested that the difference between **7** and danuphylline A (**9**) is the replacement of the carbamate CO_2Me group of **9** by a H-atom in **7**. This is in accord with the absence of the carbamate CO_2Me signals in the ^{1}H- and ^{13}C-NMR data of **7**, which are present in those of danuphylline A. Danuphylline B (**7**) is therefore the *N(1)*-decarbomethoxy derivative of danuphylline A.

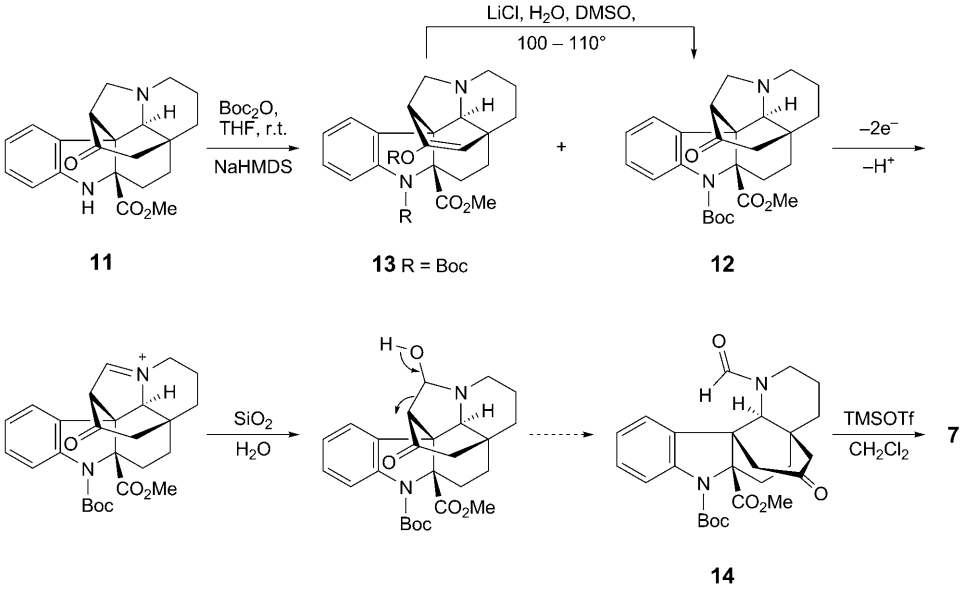
It has previously been suggested that a possible origin of the danuphylline-type alkaloids is *via* a *retro*-Aldol reaction of an unstable carbinol amine, in turn derived from hydrolysis of the iminium ion, formed from oxidation of the appropriate hexacyclic methyl chanofruticosinate precursor [21][22]. The proposal has been vindicated by the implementation of an electrochemically-mediated semisynthesis which yielded in addition to danuphylline (**8**) the lactam **10** as a minor side product [21]. Since the methyl chanofruticosinate alkaloid **11** was among the alkaloids obtained from the leaf extract [28], it was envisaged that a similar biomimetic transformation of **11** to **7** might be feasible.

Compound **11**, on electrochemical oxidation (Pt anode, 30% CH_2Cl_2/MeCN, 0.1M Et_4NClO_4), revealed two irreversible waves at 1.00 and 1.23 V *vs.* Ag/AgCl in the potential range studied. Controlled potential electrolysis (Pt gauze anode, Pt cathode) of **11** at the first potential peak (1.1 V), in the presence of 2,6-lutidine as proton scavanger, was allowed to proceed until consumption of 2 F mol^{-1} of charge. In the course of the electro-oxidation, the originally colorless solution changed to deeply orange-brown, and subsequent work-up after electrolysis as described previously [21] did not show formation of any significant product.

Our previous experience with anodic oxidation of indole derivatives [21][33–35] led us to conclude that the presence of the indolic NH in **11** may interfere in some way during the electrochemical process. We, therefore, proceeded to protect the indolic NH prior to carrying out the electrochemical oxidation. Since attempted installation of a

carbamate group on **11** with methyl chloroformate under various conditions proved problematic, and in view of the limited amount of **11** available, preparation of the N-Boc derivative was next attempted. However, this gave rise to a mixture of the desired N-Boc protected derivative **12**, accompanied by the doubly-acylated enol carbonate **13**, with the latter obtained as the major product (*e.g.* ratio of **12**:**13** *ca.* 1:2.4). Attempts to protect the C(16) C=O function prior to N-protection were unsuccessful, as were attempts to improve the yield of **12** over **13** (through varying the ratio of the reagents, changing the order of addition of the reagents, or employing lower temperatures). Fortunately, it was found that **13** could be smoothly converted to the desired **12** *via* LiCl/DMSO-mediated decarboxylation [36] (*Scheme*).

Scheme



Anodic oxidation of **12** (Pt anode, 30% CH_2Cl_2/MeCN, 0.1M Et_4NClO_4) also showed two irreversible waves at 1.07 and 1.75 V *vs.* Ag/AgCl in the potential range studied. Controlled potential electrolysis (Pt gauze anode, Pt cathode) of **12** at the first potential peak (1.2 V) in the presence of 2,6-lutidine was allowed to proceed until consumption of 2 F mol^{-1} of charge. This time, the solution remained virtually colorless during the electro-oxidation. Subsequent workup as described previously in the case of danuphylline [21], gave the Boc-protected, ring-opened product **14** in 30% yield. Finally, exposure of **14** to TMSOTf in CH_2Cl_2 [37] resulted in the cleavage of the *tert*-butoxycarbonyl group to afford danuphylline B (**7**) in 97% yield (*Scheme*). As in the case of **11**, attempted installation of the carbamate function on **9** proved to be not a straightforward process, and due to paucity of material, conversion of **11** or **14** to **8** could not be carried out.

We would like to thank the University of Malaya, the Academy of Science, Malaysia (SAGA), and MOHE, Malaysia (FRGS), for financial support.

Experimental Part

1. *General.* All air-moisture-sensitive reactions were carried out under N_2 in oven-dried glassware. THF was freshly distilled from Na/benzophenone, and MeCN and CH_2Cl_2 from CaH_2, under N_2. All other reagents were used without further purification. All electrochemical experiments were performed on a *BAS 100B* electrochemical analysis system using a 100 ml cylindrical glass cell (*BAS MR-1195*) fitted with a *Teflon* cell top. The electrodes used for cyclic voltammetry were Pt wire electrode (1.6 mm diameter), with Pt as the counter-electrode and Ag/AgCl/NaCl (3M) as the reference electrode. Preparative electrolyses were performed with a Pt gauze electrode (diameter 4 cm, height 5 cm). CC: Column chromatography. Optical rotations: *Jasco P-1020* digital polarimeter. UV Spectra: *Shimadzu UV-3101PC* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Perkin-Elmer 1600* FT-IR spectrophotometer in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Jeol JNM-LA-400* spectrometer at 400 and 100 MHz, resp.; $CDCl_3$ solns. with Me_4Si as internal standard; δ in ppm, J in Hz. MS measurements were carried out at OIC Organic Mass Spectrometry, University of Tasmania, Tasmania, Australia.

2. *Plant Material*. The plant material was collected in Petaling Jaya, Malaysia (May, 2003), and was identified by Dr. *David Middleton*, Herbarium, Royal Botanic Garden, Edinburgh, 20A Inverleith Row, EH3 5LR Scotland. Herbarium voucher specimens (K 668) are deposited with the Herbarium, University of Malaya, Kuala Lumpur, Malaysia and at Edinburgh.

3. *Extraction and Isolation*. Extraction of the ground leaf material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere [38]. The alkaloids were isolated by initial CC (SiO_2, $CHCl_3$ with increasing proportions of MeOH), followed by rechromatography of the appropriate partially resolved fractions using CC or centrifugal TLC. Initial CC of the basic fraction from the leaf provided essentially eight fractions. 12-Methoxykopsine (**6**; 8.7 mg kg^{-1}) was obtained from *Fr. 4*, after CC (SiO_2, $CHCl_3$/MeOH) and centrifugal TLC (SiO_2, AcOEt/hexanes). Two successive centrifugal TLC (SiO_2, Et_2O/hexanes, 0.5% NH_3) of *Fr. 5* provided danuphylline B (**7**; 1.0 mg kg^{-1}).

12-Methoxykopsine (= *Methyl (3α)-3-Hydroxy-17-methoxy-22-oxokopsan-1-carboxylate*; **6**). Colorless oil. $[\alpha]_D = +16$ ($c = 0.05$, $CHCl_3$). UV (EtOH): 215 (4.58), 244 (4.05), 289 (3.52). IR (dry film): 3422, 1753, 1678. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 410 (22, M^+), 382 (9, $[M - CH_2CH_2]^+$), 353 (4), 312 (100, $[M - C_5H_4O_2]^+$), 253 (12), 83 (6), 40 (10). HR-EI-MS: 410.1842 ($C_{23}H_{26}N_2O_5^+$; calc. 410.1842).

Danuphylline B (= *Methyl (4a*R*,6a*S*,11b*S*,11c*S*)-1-Formyl-1,3,4,5,6,11c-hexahydro-13-oxo-2*H*-4a,11b-propanopyrido[3,2-*c*]carbazole-6a(7*H*)-carboxylate*; **7**). Colorless oil. $[\alpha]_D = +47$ ($c = 0.13$, $CHCl_3$). UV (EtOH): 212 (4.02), 239 (3.68), 294 (3.34). IR (dry film): 3347, 1731, 1661. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 368 (7, M^+), 339 (7, $[M - CHO]^+$), 309 (100, $[M - CO_2Me]^+$), 281 (19, $[M - CO_2Me - CH_2CH_2]^+$), 252 (29), 224 (11), 188 (6), 156 (10), 124 (20), 96 (17), 83 (8), 40 (24). HR-EI-MS: 368.1735 ($C_{21}H_{24}N_2O_4^+$; calc. 368.1736).

4. *Starting Material. Methyl* N-*De(methoxycarbonyl)chanofruticosinate* (**11**) was obtained from *K. arborea* as described previously [28][39].

Preparation of **12** *and* **13**. To a stirred soln. of **11** (33.5 mg, 0.095 mmol), Boc_2O (103.8 mg, 0.48 mmol), and THF (5 ml) at r.t. was added dropwise NaHMDS (200 µl, 1.0M), and the mixture was stirred for 45 min at r.t. The mixture was quenched with sat. NH_4Cl soln. (15 ml), and extracted with CH_2Cl_2 (3×20 ml). The combined org. layers were dried (Na_2SO_4), the solvent evaporated, and the residue purified by centrifugal TLC (SiO_2, hexanes/AcOEt 5:3) to give 11.1 mg (26%) of **12** and 32.5 mg (62%) of **13**.

Methyl (2β,11β,12β,19α)-21-Oxo-11,21-cycloaspidospermidine-2-carboxylate (**12**). Colorless oil. $[\alpha]_D = +106$ ($c = 0.65$, $CHCl_3$). IR (dry film): 1744, 1711. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.78 (br. *d*, $J = 8$, H–C(12)); 7.32 (*dd*, $J = 8, 1$, H–C(9)); 7.21 (*td*, $J = 8, 1$, H–C(11)); 6.96 (*td*, $J = 8, 1$, H–C(10)); 3.57 (*s*, CO_2Me); 3.16 (*dd*, $J = 11.5, 6.5$, H–C(5)); 2.97 (*d*, $J = 6$, H–C(3)); 2.90–3.02 (*m*, H–C(3)); 2.78 (*d*, $J = 11.5$, H–C(5)); 2.71 (*d*, $J = 19.5$, H–C(17)); 2.54–2.62 (*m*, H–C(18)); 2.50 (*s*, H–C(21)); 2.38–

2.45 (*m*, H–C(18)); 2.28 (*d*, *J* = 6.5, H–C(6)); 2.15 (*d*, *J* = 19.5, H–C(17)); 1.78–1.88 (*m*, H–C(19)); 1.63–1.66 (*m*, H–C(15)); 1.59–1.62 (*m*, H–C(14)); 1.50 (*s*, NCO_2CMe_3); 1.43–1.45 (*m*, H–C(14)); 1.27–1.37 (*m*, H–C(15)); 1.27–1.37 (*m*, H–C(19)). ^{13}C-NMR (100 MHz, $CDCl_3$): 208.2 (C(16)); 171.1 (CO_2Me); 152.4 (NCO_2CMe_3); 141.6 (C(13)); 133.4 (C(8)); 128.4 (C(11)); 124.9 (C(9)); 122.6 (C(10)); 114.1 (C(12)); 82.4 (NCO_2CMe_3); 73.2 (C(2)); 67.6 (C(21)); 57.6 (C(7)); 56.9 (C(6)); 52.1 (C(5)); 52.0 (CO_2Me); 46.4 (C(3)); 43.7 (C(17)); 36.3 (C(20)); 35.6 (C(15)); 34.4 (C(19)); 28.2 (NCO_2CMe_3); 25.1 (C(18)); 17.3 (C(14)). EI-MS: 452 (3, M^+), 293 (100), 249 (2), 222 (5), 180 (3). HR-EI-MS: 452.2316 ($C_{26}H_{32}N_2O_5^+$; calc. 452.2311).

*1-(*tert*-Butyl) 2-Methyl (2β,11β,12β,19α)-21-Oxo-11,21-cycloaspidospermidine-1,2-dicarboxylate* (**13**). $[\alpha]_D = +99$ ($c = 0.71$, $CHCl_3$). IR (dry film): 1811, 1752, 1708. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.79–8.06 (br. *s*, H–C(12)); 7.67 (*d*, *J* = 8, H–C(9)); 7.24 (*t*, *J* = 8, H–C(11)); 7.01 (*t*, *J* = 8, H–C(10)); 4.82 (*s*, H-C(17)); 3.74 (*s*, CO_2Me); 3.66 (*dd*, *J* = 10, 5, H–C(5′)); 3.21 (*d*, *J* = 10, H–C(5)); 2.99 (*t*, *J* = 14, H–C(3)); 2.92 (*t*, *J* = 14, H–C(3)); 2.73 (*s*, H–C(21)); 2.56 (*d*, *J* = 5, H–C(6)); 1.82–1.91 (*m*, H–C(15)); 1.82–1.91 (*m*, H–C(19)); 1.59–1.74 (*m*, H–C(14)); 1.52 (*s*, NCO_2CMe_3); 1.47 (*s*, OCO_2CMe_3); 1.38–1.41 (*m*, H–C(19)); 1.32–1.35 (*m*, H–C(15)); 1.22–1.28 (*m*, H–C(14)). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.4 (CO_2Me); 151.2 (C(16)); 150.1 (NCO_2CMe_3); 150.1 (OCO_2CMe_3); 140.9 (C(13)); 132.8 (C(8)); 128.4 (C(11)); 126.0 (C(9)); 122.9 (C(10)); 120.7 (C(17)); 114.5 (C(12)); 82.6 (NCO_2CMe_3); 82.0 (OCO_2CMe_3); 73.0 (C(2)); 64.5 (C(21)); 60.9 (C(7)); 57.9 (C5)); 51.5 (CO_2Me); 48.0 (C(3)); 47.2 (C(6)); 37.5 (C(15)); 36.7 (C(20)); 31.6 (C(19)); 28.1 (NCO_2CMe_3); 27.7 (OCO_2CMe_3); 26.5 (C(18)); 19.2 (C(14)). EI-MS: 552 (5, M^+), 435 (7), 393 (15), 337 (21), 263 (4), 222 (8), 180 (5), 144 (3). HR-EI-MS: 552.2837 ($C_{31}H_{40}N_2O_7^+$; calc. 552.2836).

5. *Decarboxylation of* **13**. A mixture of **13** (13.5 mg, 0.024 mmol), LiCl (2.0 mg, 0.048 mmol), H_2O (0.1 g), and DMSO (4 ml) was stirred at 100–110° for 6 h. The mixture was cooled in ice, and then H_2O (40 ml) was added, followed by brine (3 ml). The mixture was extracted with CH_2Cl_2 (3 × 30 ml), and the combined CH_2Cl_2 extracts were then washed with sat. NaCl soln., dried (Na_2SO_4), the solvent was evaporated, and the residue purified by centrifugal TLC (SiO_2, hexanes/AcOEt 5:3) to give 7.0 mg (61%) of **12**.

6. *Anodic Oxidation of* **12**. A soln. of **12** (12.4 mg, 0.02 mmol) in 50 ml of a mixed solvent (30% CH_2Cl_2/MeCN) containing Et_4NClO_4 (0.1M) and 2,6-lutidine (0.2 mmol) was placed in a divided cell under N_2. The anodic potential (Pt gauze) was maintained at 1.2 V *vs.* Ag/AgCl, and the electrolysis continued until 2 F mol^{-1} were transferred. The progress of electrolysis was also monitored by cyclic voltammetry. The soln. was then evaporated to dryness, and CH_2Cl_2 (12 ml) was added. The precipitated electrolyte was then filtered off, and the residue washed with CH_2Cl_2. The CH_2Cl_2 extract was then chromatographed over SiO_2 (CH_2Cl_2) *via* centrifugal TLC to afford **14** (3.7 mg, 30 %). Colorless oil. $[\alpha]_D = +28$ ($c = 0.39$, $CHCl_3$). IR (dry film): 1738, 1712, 1673. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 (br. *d*, *J* = 7.5, H–C(12)); 7.31 (*t*, *J* = 7.5, H–C(9)); 7.04 (*t*, *J* = 7.5, H–C(11)); 6.88 (*d*, *J* = 7.5, H–C(10)); 6.38 (*s*, H–C(5)); 4.52 (*dd*, *J* = 14, 9, H–C(3)); 3.57 (*s*, CO_2Me); 3.34 (*s*, H–C(21)); 3.20 (br. *d*, *J* = 16.5, H–C(18)); 2.83 (*d*, *J* = 17, H–C(6)); 2.69–2.77 (*m*, H–C(3)); 2.71 (*d*, *J* = 20, H–C(17)); 2.47–2.55 (*m*, H–C(18)); 2.50 (*d*, *J* = 20, H–C(17)); 2.37 (*d*, *J* = 17, H–C(6)); 1.87–2.00 (*m*, H–C(14)); 1.69–1.79 (*m*, H–C(14)); 1.66–1.79 (*m*, H–C(15)); 1.66–1.79 (*m*, H–C(19)); 1.58–1.62 (*m*, H–C(19)); 1.58 (*s*, NCO_2CMe_3); 1.23–1.31 (*m*, H–C(15)). ^{13}C-NMR: 207.0 (C(16)); 170.7 (CO_2Me); 165.8 (C(5)); 153.6 (NCO_2CMe_3); 143.7 (C(13)); 129.8 (C(9)); 129.2 (C(8)); 123.8 (C(10)); 122.8 (C(11)); 115.5 (C(12)); 83.1 (NCO_2CMe_3); 78.6 (C(2)); 62.2 (C(21)); 54.1 (C(7)); 52.7 (CO_2Me); 46.1 (C(17)); 39.4 (C(6)); 39.4 (C(19)); 35.0 (C(3)); 34.4 (C(20)); 29.9 (C(15)); 28.4 (NCO_2CMe_3); 23.7 (C(18)); 19.4 (C(14)). EI-MS: 468 (2, M^+), 368 (10), 309 (100), 281 (11), 252 (14), 222 (7), 180 (4), 156 (7). HR-EI-MS: 468.2260 ($C_{26}H_{32}N_2O_6^+$; calc. 468.2260).

7. *Removal of the Boc Group from* **14**. Neat TMSOTf (11 µl, 0.061 mmol) was added dropwise to a soln. of **14** (6 mg, 0.013 mmol) and CH_2Cl_2 (5 ml) at r.t. The flask was left open to air so that adventitious H_2O would create a small amount of triflic acid. After 3 h, the soln. was partitioned between sat. Na_2CO_3 soln. (15 ml) and CH_2Cl_2 (15 ml). The phases were separated, and the aq. phase were extracted with CH_2Cl_2 (3 × 15 ml). The combined org. layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by centrifugal TLC (SiO_2, hexanes/AcOEt 5:3) to give 4.6 mg (97%) of **7**.

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